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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/063,519	Applicant(s) EATON ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. Claims 1-6 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, paragraph 205. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Information Disclosure Statement

3. The information disclosure statement submitted on 10 September 2002 has been considered by the examiner. However, since the Blast results cited therein are not true publications with a publication date, they are not fully in compliance with 37 CFR 1.97 and thus they will not be printed on the face of the patent issuing from this application.

Claim Rejections - 35 USC § 112

Art Unit: 1642

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 6 are indefinite for reciting "an antibody that binds" in claim 39 and "the antibody of claim 39 which specifically binds" in claim 44 because the exact meaning is unclear. It is not clear what the difference between the two claims is and what each claim is meant to encompass, given that antibody binding is determined by the variable regions structure and is a "specific" interaction.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 1-6 are directed to an antibody that binds SEQ ID NO:14. The specification discloses the isolation of a nucleic acid, SEQ ID NO:13, which encodes a protein, SEQ ID NO:14 which is disclosed as PRO 1864 (see Figure 13 and 14). The DNA of SEQ ID NO:13 is disclosed to be over expressed in melanoma vs. normal skin but the protein is not disclosed to be expressed (see page 141).

The specification does not disclose that the polypeptide has any homology with known, characterized polypeptides. The instant specification does not disclose any additional information regarding PRO1864 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1864, and what physiological significance PRO1864 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

The specification generally asserts that all of the disclosed PRO polypeptides will be useful for a number of purposes, however, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. The asserted utilities will each be addressed in turn.

1) the PRO polypeptide can be used to isolate other polypeptides to which it binds (paragraph 0329): This asserted utility is not specific or substantial. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed

Art Unit: 1642

PRO1864 polypeptides. Furthermore, since the specification does not disclose how PRO1864 or its binding partners can be used, significant further research would be required of the skilled artisan to determine how to use the claimed polypeptide or its binding partner. Since the asserted utility is not presented in a ready to use, real-world application, the asserted utility is not substantial.

2) the PRO polypeptide can be used as a molecular weight marker (paragraph 0334): This asserted utility is not specific. Since the same can be done with any polypeptide, the asserted utility is not specific to the claimed PRO1864 polypeptides.

3) the PRO polypeptide can be used in tissue typing (paragraph 0336): This asserted utility is not specific or substantial. With the exception of a few housekeeping genes, all polypeptides have a tissue specific pattern of expression, and thus virtually any polypeptide can be used in tissue typing. Thus, the asserted utility is not specific to PRO1864.

4) the PRO polypeptide can be used in therapy (paragraph 0337): This asserted utility is not specific or substantial. Since a defect in any polypeptide is likely to cause a disease of some sort, every polypeptide is a target for drug development. Thus, the asserted utility is not specific to the claimed PRO1864 polypeptide. Furthermore, the specification does not disclose a nexus between any specific disease states and a change in amount or form of PRO1864. Significant further research would have to be conducted to identify such a nexus. Therefore, the asserted utility is not substantial.

5) the PRO polypeptide can be used to identify agonists or antagonists (paragraph 0345): Since the same can be done with any polypeptide, the asserted utility

Art Unit: 1642

is not specific to the claimed PRO1864 polypeptides. Furthermore, since no activity has been assigned to PRO1864, the assays cannot be conducted until the specific biological activities of PRO1864 are determined empirically. Therefore, the asserted utility is also not substantial.

The specification also discloses that PRO1864 tested positive in a microarray analysis to detect over-expression of PRO polypeptides in cancerous tumors (Example 18, pp. 140). This information does not provide a credible, specific and substantial utility for PRO1864 nucleic acids, polypeptides or antibodies. PRO1864 mRNA levels are indicated as being over-expressed in melanoma tumor as compared to a normal skin. The data is not presented to indicate such overexpression or how it was determined. This is very vague, and does not disclose what mathematical calculations were used to establish significance. Therefore, the data presented in the microarray assay are preliminary at best, and cannot be evaluated or repeated independently by the skilled artisan. Clearly, further research would be required of the skilled artisan to establish whether and how a probe used in the microarray assay could be used as diagnostic markers or therapeutic targets. Such further experimentation indicates that the asserted utility is not in currently available form.

Furthermore, the literature indicates that such results are to be evaluated very critically. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change

Art Unit: 1642

or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Finally, increased transcription does not always correlate with increased polypeptide levels. See Haynes et al. (1998, Electrophoresis 1921862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that increased transcription results in increased polypeptide levels.

Thus, the proposed use of the PRO1864 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[I]t is not a reward for the search, but compensation for its successful

conclusion."

Therefore since the polypeptide of SEQ ID NO:14 has no substantial utility, the antibody to SEQ ID NO:14 also does not have a substantial utility.

8. Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Claims 1-5, 12-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a antibodies that bind to SEQ ID NO:14. The specification discloses the polynucleotide is overexpressed in melanoma tumor as compared to a normal skin. The specification does not teach that the polypeptide is over expressed in any disease state. Thus one would not know how to use the claimed antibody when the polypeptide is not disclosed as being expressed.

The specification does not disclose that the protein is overexpressed in any disease state, the specification states that the DNA of SEQ ID NO:13 is over expressed in melanoma vs normal skin. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. In addition, Pennica et al (PNAS

Art Unit: 1642

95:14717-22, 1998) teach that the copy number is amplified but the RNA expression is actually reduced. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic and the use of an antibody to SEQ ID NO:14 are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would be unable to predictably use the antibodies in any diagnostic setting without undue experimentation.

In view of the lack of guidance, lack of examples, and lack of predictability in the art and the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

10. No claim is allowed.


Art Unit: 1642

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Larry R. Helms

571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER